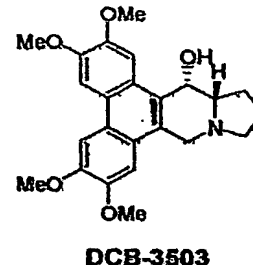
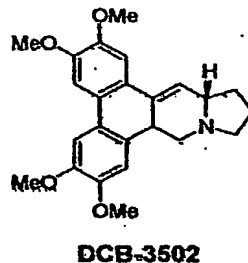
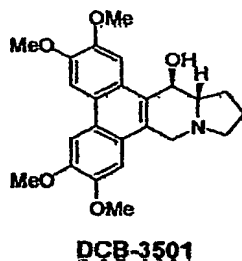
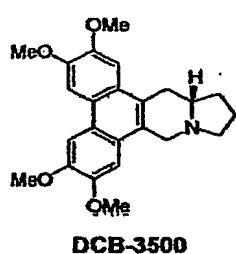


FIGURE 1

**Table 1. Growth inhibition and loss of clonogenicity of KB (human nasopharyngeal carcinoma) and HepG2 (hepatocyte carcinoma) cells.**

**A. Chemical structure**



**B. EC50 (growth inhibition)**

cell line	DCB-3500 ( $\mu\text{M}$ )	DCB-3501 ( $\mu\text{M}$ )	DCB-3502 ( $\mu\text{M}$ )	DCB-3503 ( $\mu\text{M}$ )
KB	0.012 $\pm$ 0.003	0.106 $\pm$ 0.084	0.234 $\pm$ 0.091	0.028 $\pm$ 0.004
HepG2	0.011 $\pm$ 0.004	0.110 $\pm$ 0.045	0.264 $\pm$ 0.115	0.035 $\pm$ 0.005

**C. LD50 (colony forming ability)**

cell line	DCB-3500 ( $\mu\text{M}$ )	DCB-3501 ( $\mu\text{M}$ )	DCB-3502 ( $\mu\text{M}$ )	DCB-3503 ( $\mu\text{M}$ )
KB	0.83 $\pm$ 0.31	3.07 $\pm$ 1.17	6.29 $\pm$ 3.74	1.55 $\pm$ 0.47
HepG2	0.04 $\pm$ 0.006	0.21 $\pm$ 0.13	0.45 $\pm$ 0.13	0.17 $\pm$ 0.08

## FIGURE 1 CONT'D

**Table 2. EC50 of DCB-3500, 3501, 3502 and 3503 on the growth inhibition of KB cells and its drug resistant cells.**

## A. EC50

Cell line	DCB-3500 ( $\mu$ M)	DCB-3501 ( $\mu$ M)	DCB-3502 ( $\mu$ M)	DCB-3503 ( $\mu$ M)
KB	0.012 $\pm$ 0.003	0.106 $\pm$ 0.084	0.234 $\pm$ 0.091	0.028 $\pm$ 0.004
KB-MDR	0.014 $\pm$ 0.005	0.143 $\pm$ 0.082	0.282 $\pm$ 0.138	0.026 $\pm$ 0.008
KB-7D	0.012 $\pm$ 0.007	0.225 $\pm$ 0.206	0.527 $\pm$ 0.080	0.045 $\pm$ 0.010
KB-7D-Rev	0.011 $\pm$ 0.006	0.070 $\pm$ 0.057	0.289 $\pm$ 0.188	0.025 $\pm$ 0.010
KB-Hu-R	0.025 $\pm$ 0.007	0.070 $\pm$ 0.042	0.218 $\pm$ 0.167	0.036 $\pm$ 0.006
KB-Hu-Rev	0.016 $\pm$ 0.004	0.045 $\pm$ 0.004	0.127 $\pm$ 0.095	0.028 $\pm$ 0.016
KB-100	0.020 $\pm$ 0.010	0.103 $\pm$ 0.033	0.179 $\pm$ 0.063	0.038 $\pm$ 0.001
KB-100-Rev	0.010 $\pm$ 0.003	0.118 $\pm$ 0.031	0.247 $\pm$ 0.122	0.041 $\pm$ 0.009

## B. Description of resistant cell lines

Cell line	Biochemical changes	Resistant to
KB-MDR	gp 170 $\uparrow$	VP-16, Taxol, Adrimycin, Vincristine
KB-7D	Topo II $\downarrow$ , MRP $\uparrow$	VP-16, Vincristine, Adrimycin
KB-7D-Rev	Topo II $\downarrow$	VP-16, Adrimycin
KB-Hu-R	Ribonucleotide reductase $\uparrow$ CdR kinase $\downarrow$	Hydroxyurea, AraC, Gemcitabine
KB-Hu-Rev	CdR kinase $\downarrow$	AraC, Gemcitabine
KB-100	Topo I $\downarrow$ XRCC 1 $\uparrow$	camptothecin, topotecan, SN-38
KB-100-Rev	Topo I $\downarrow$ XRCC 1 $\uparrow$	camptothecin, topotecan, SN-38

## FIGURE 1 CONT'D

Table 3. Impact of DCB-3500 and 3503 on cell cycle progression

KB		G0-G1	S	G2-M
Control	24 h	75	10	15
Nocodazole		0	10	90
3500 0.03 uM		62	19	19
3500 0.1 uM		56	26	18
3500 0.3 uM		54	30	16
3500 1 uM		52	36	12
3503 0.1 uM		68	18	14
3503 0.3 uM		52	33	15
3503 1 uM		63	24	13
3503 3 uM		57	30	13

HepG2		G0-G1	S	G2-M
Control	24 h	45	27	28
Nocodazole		2	18	80
00 0.03 uM		47	29	24
00 0.1 uM		44	33	23
00 0.3 uM		51	21	28
00 1 uM		41	27	32
03 0.1 uM		50	26	24
03 0.3 uM		55	20	25
03 1 uM		53	21	26
03 3 uM		47	25	28

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FIGURE 1 A

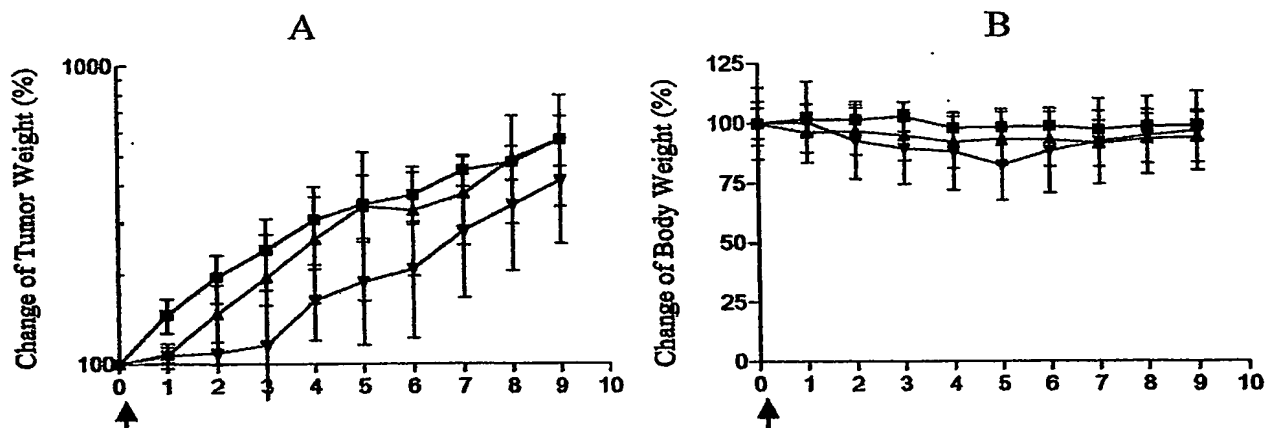
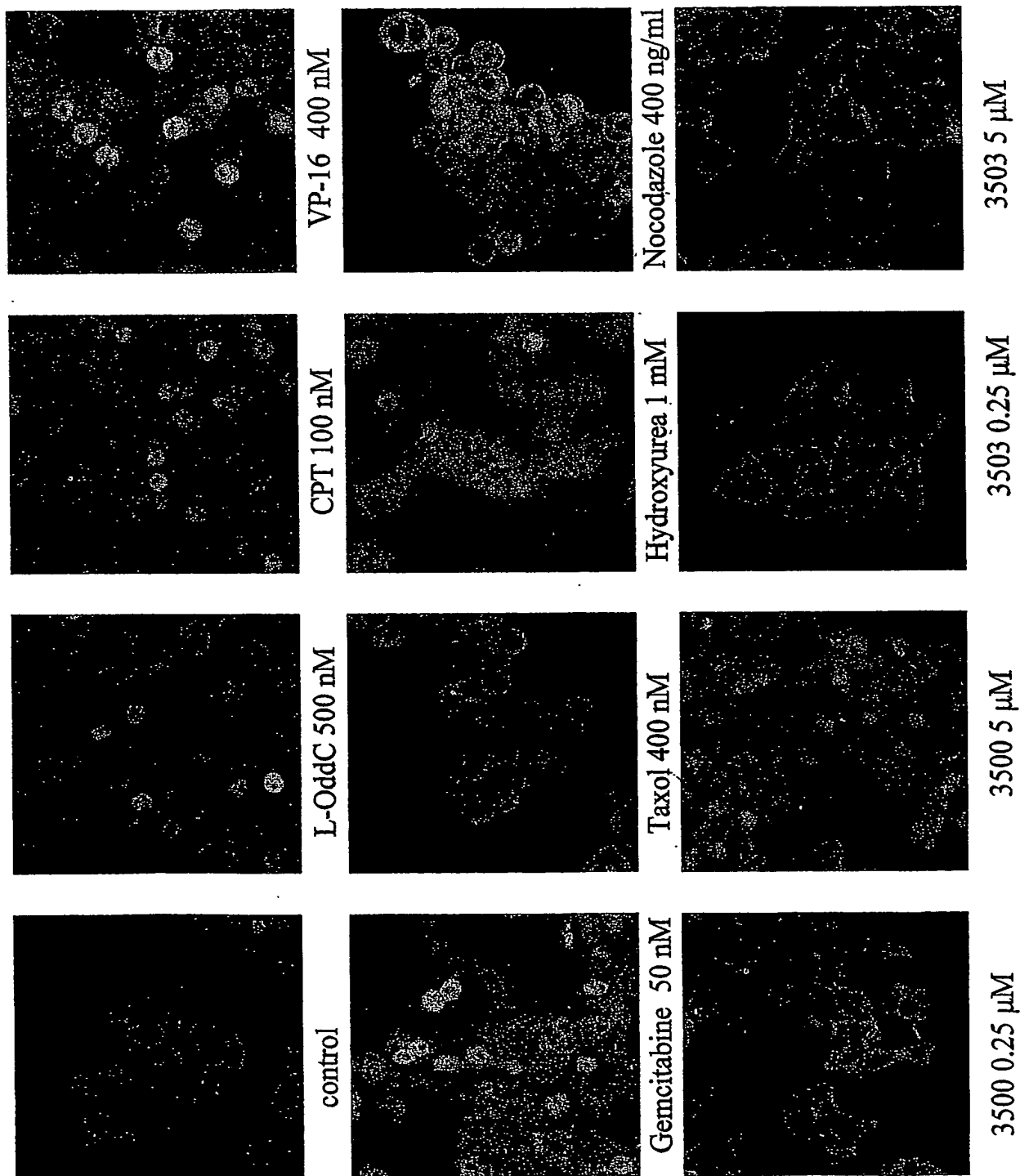


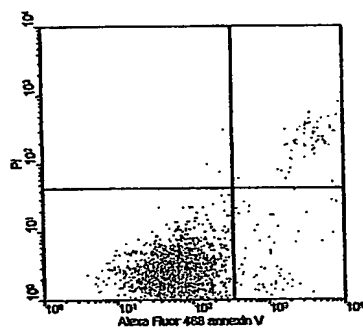
FIGURE 2

# Regulation of p53 in response to conventional chemotherapeutic drugs and 3500, 3503 in KB cells

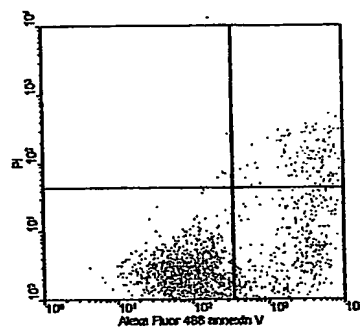


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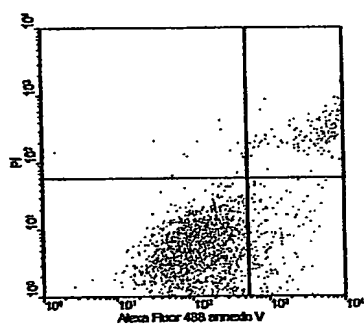
FIGURE 3



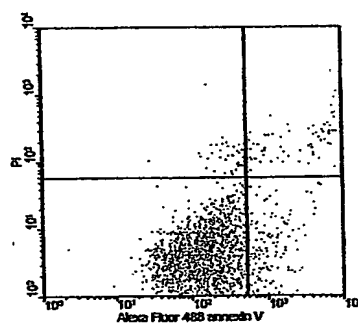
KB untreated



KB 3503 3µM



HepG2 untreated



HepG2 3503 3µM

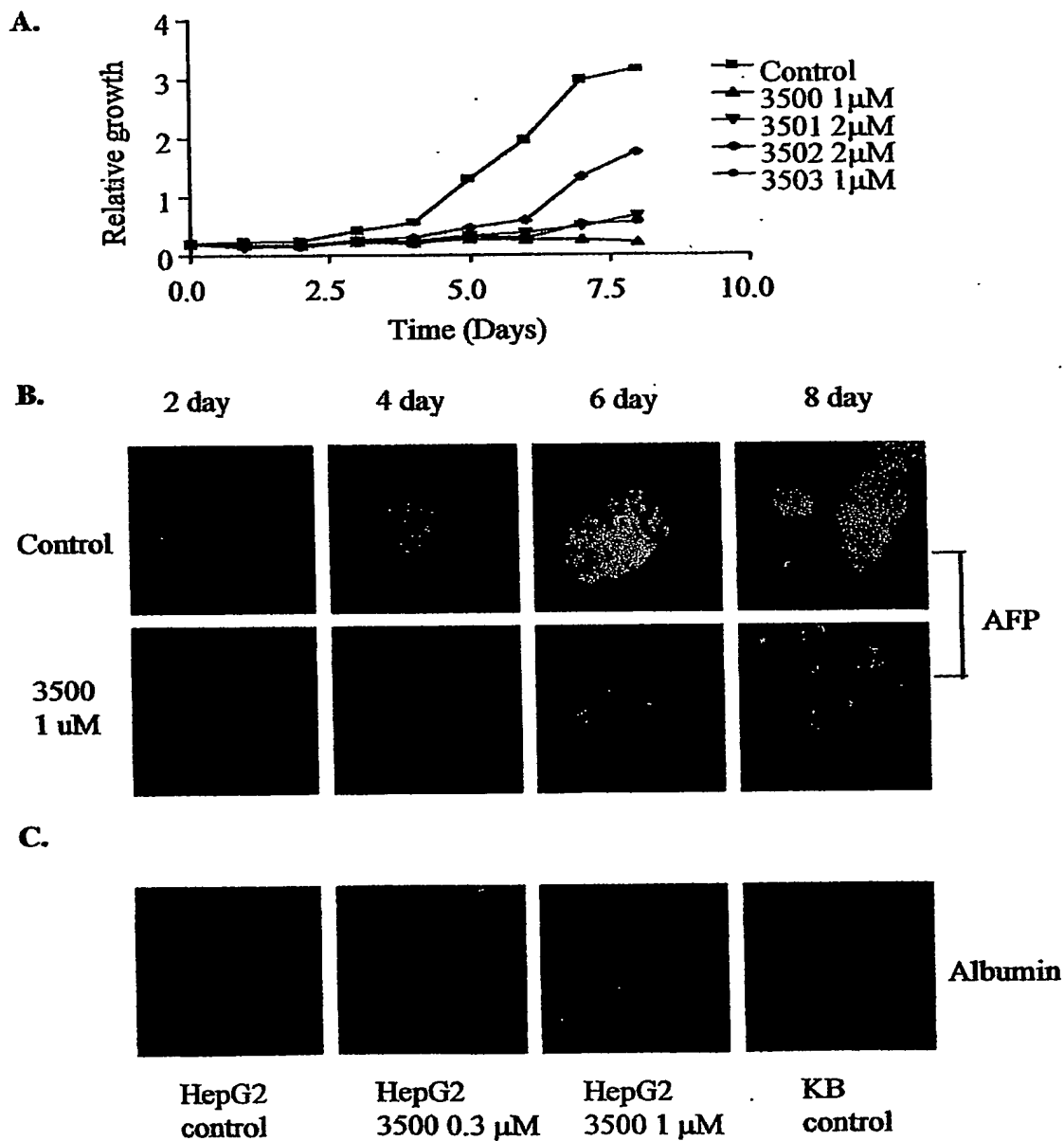
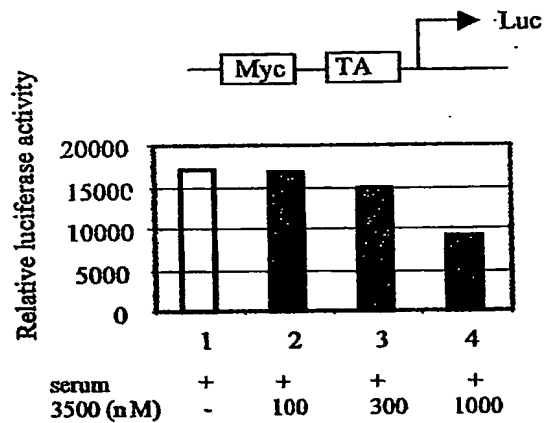
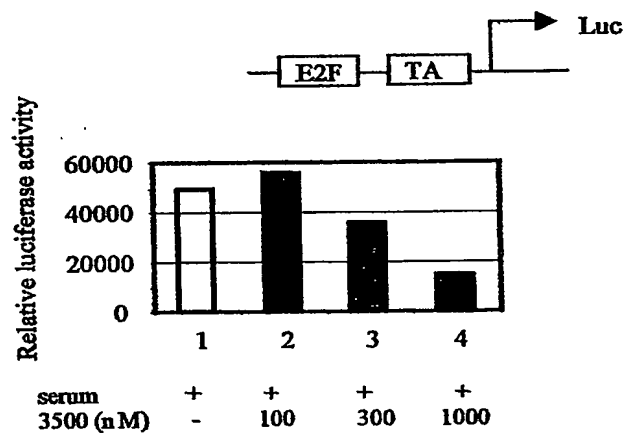
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FIGURE 4

FIGURE 5

A.



B.

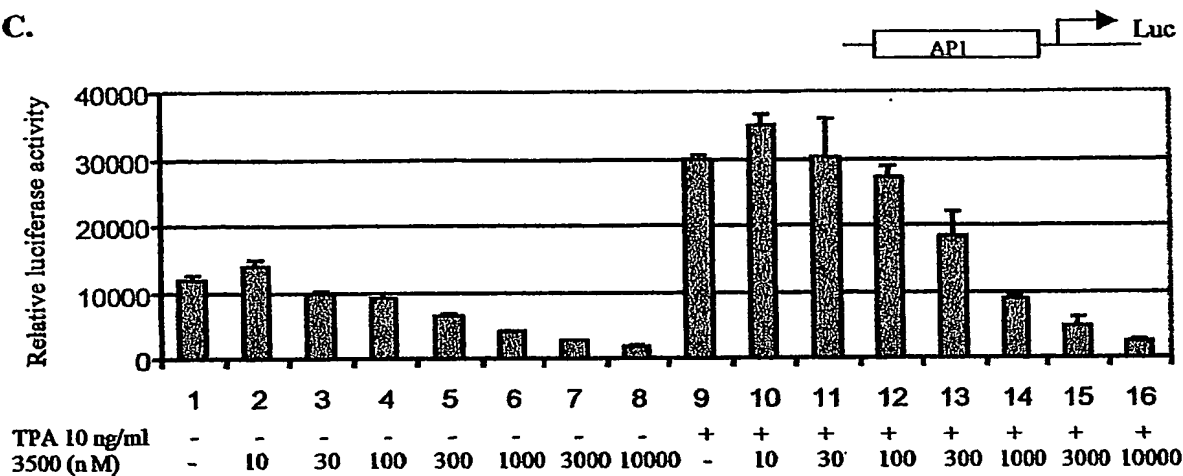




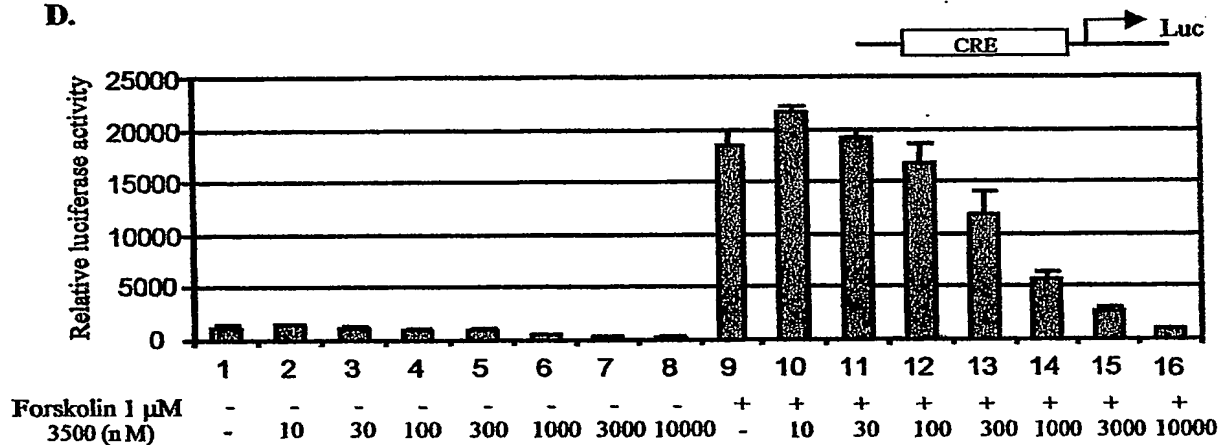
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FIGURE 5 CONT'D

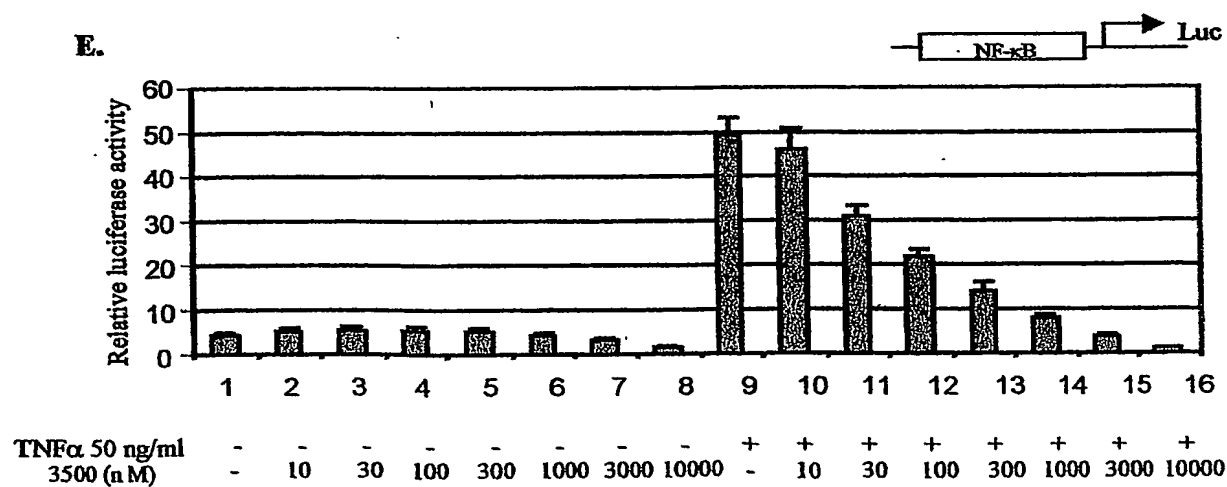
C.



D.



E.



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FIGURE 5 CONT'D

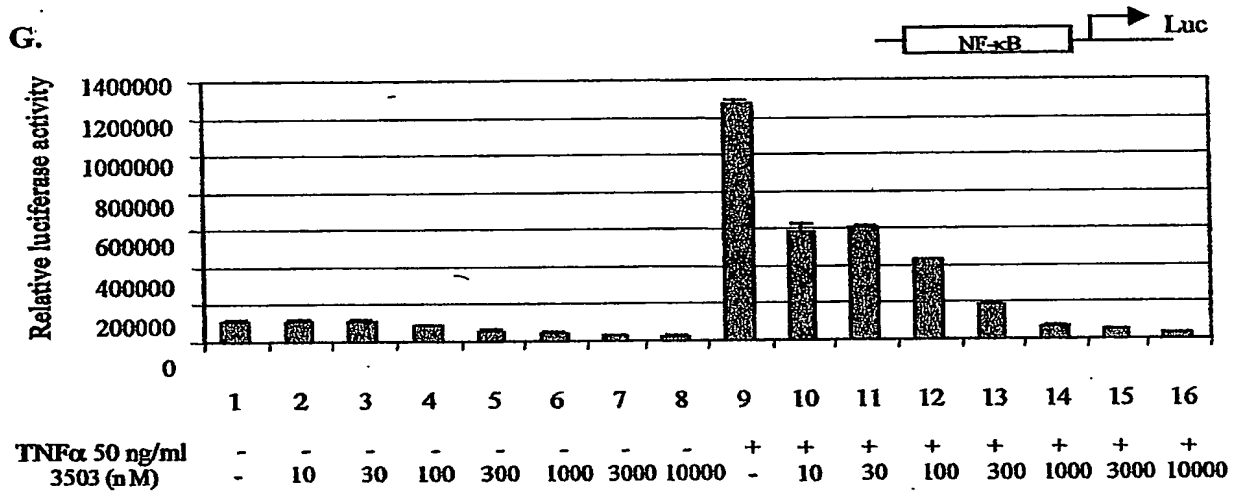
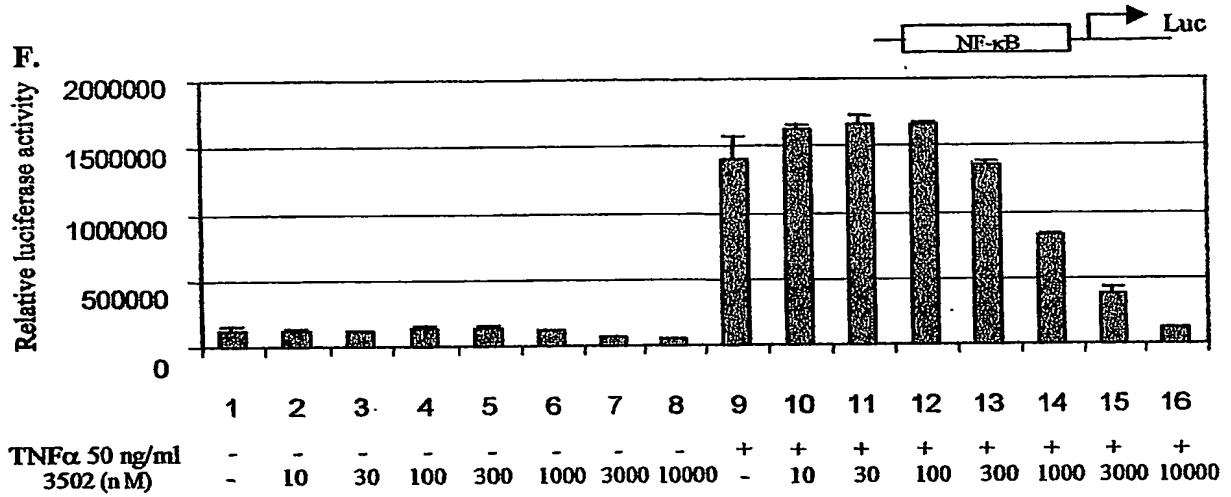


FIGURE 6

Scheme I

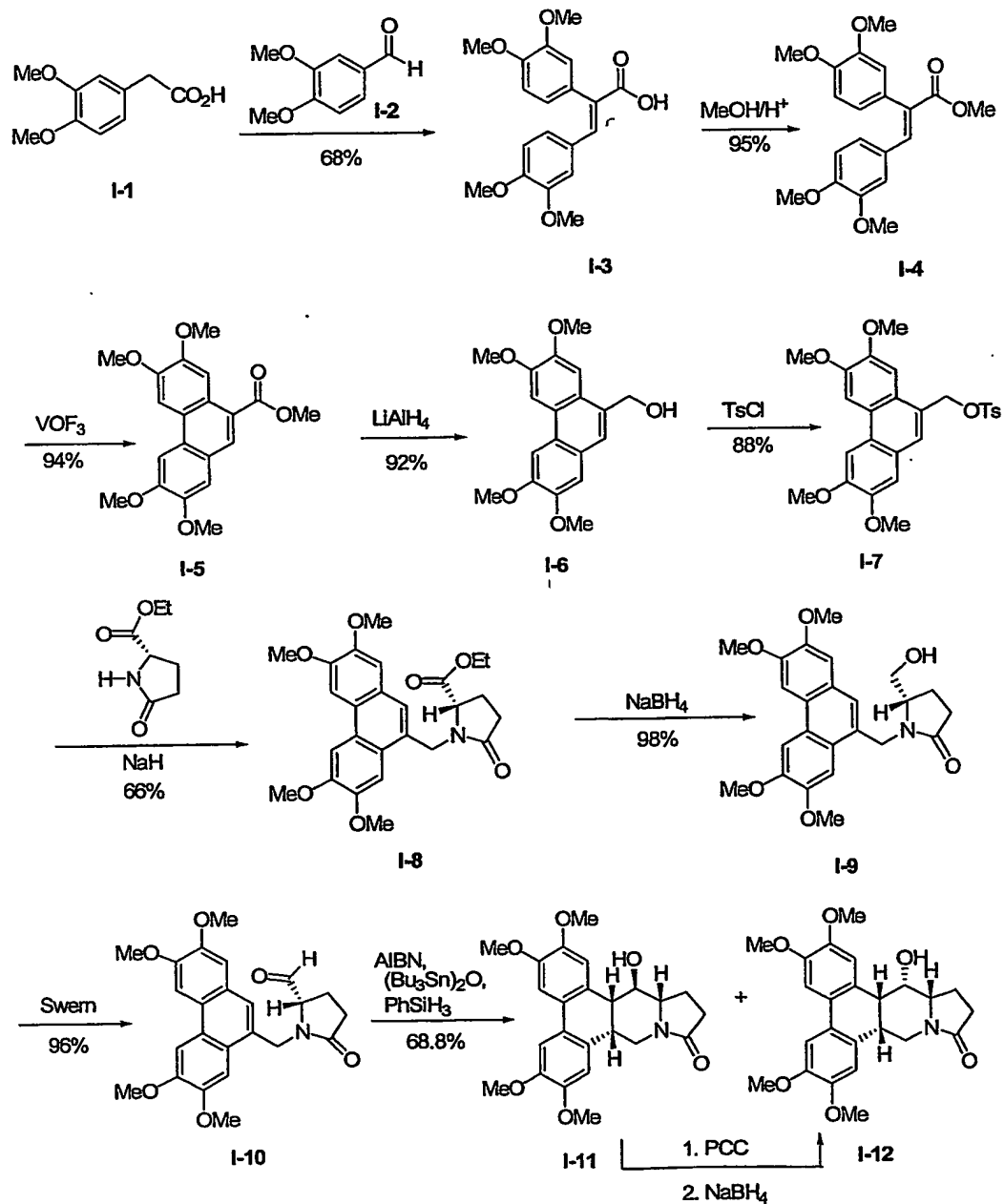


FIGURE 7

Scheme II

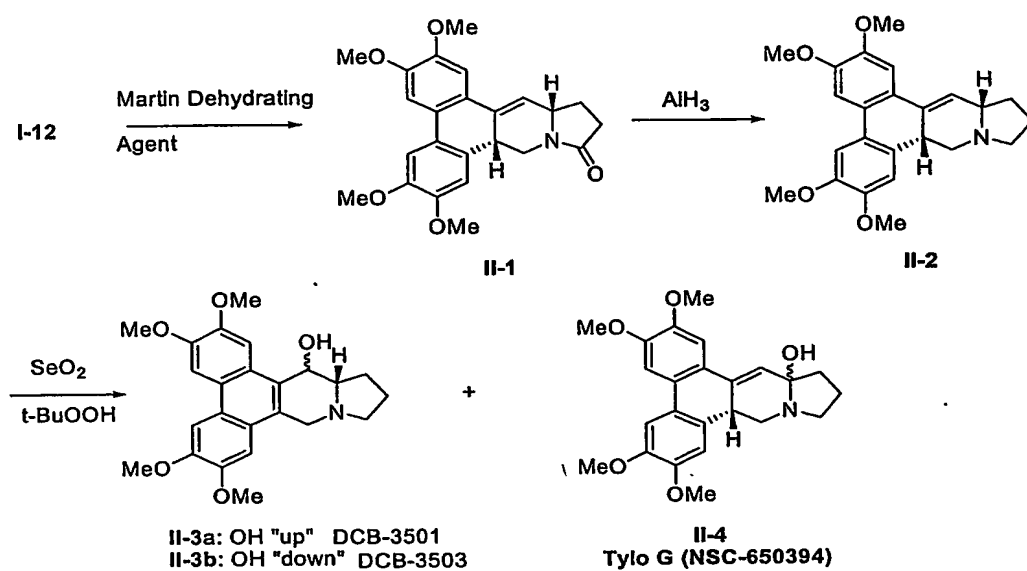


FIGURE 8

## Scheme III

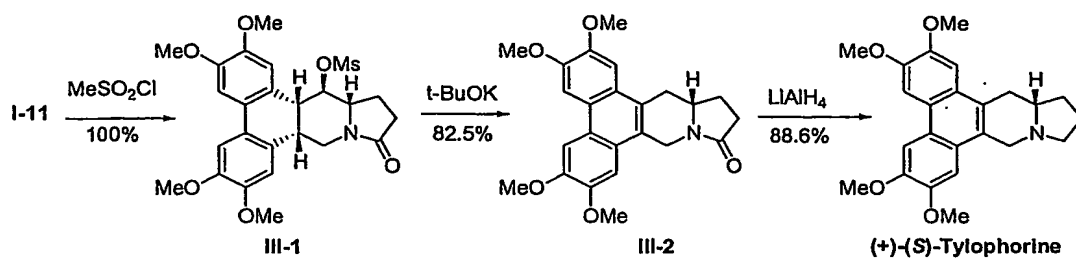
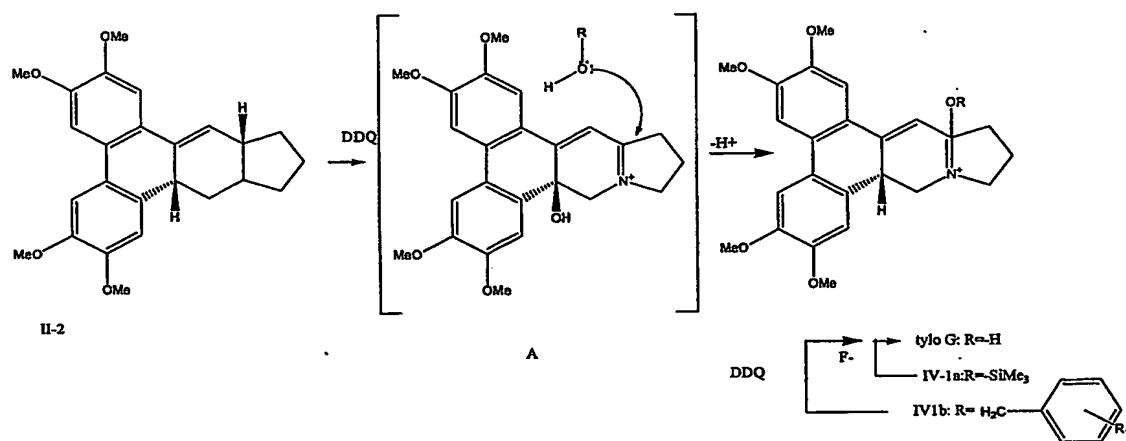


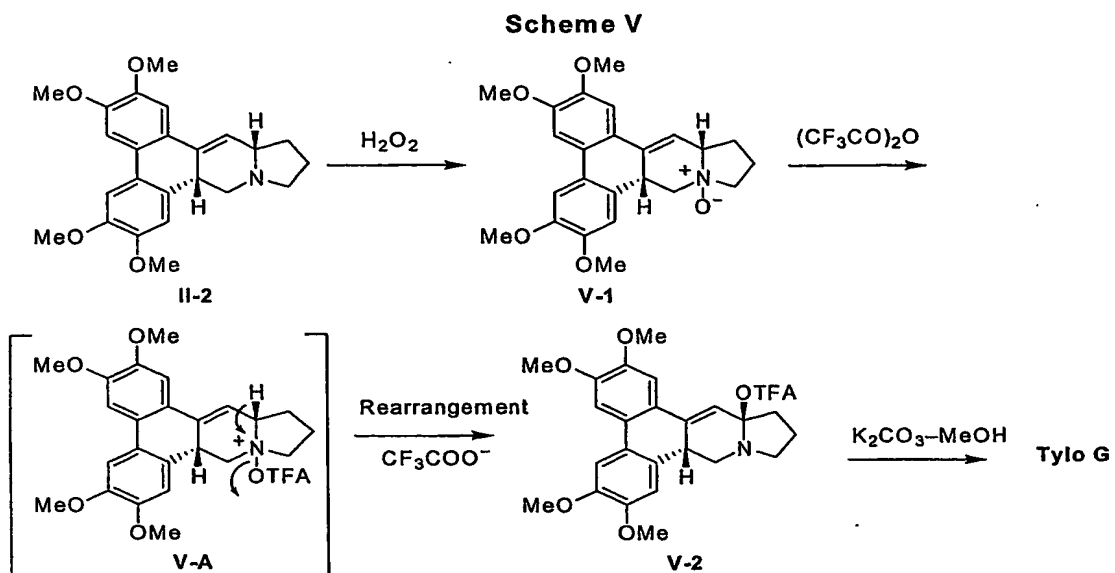
FIGURE 9

Scheme IV



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FIGURE 10



## Scheme VI

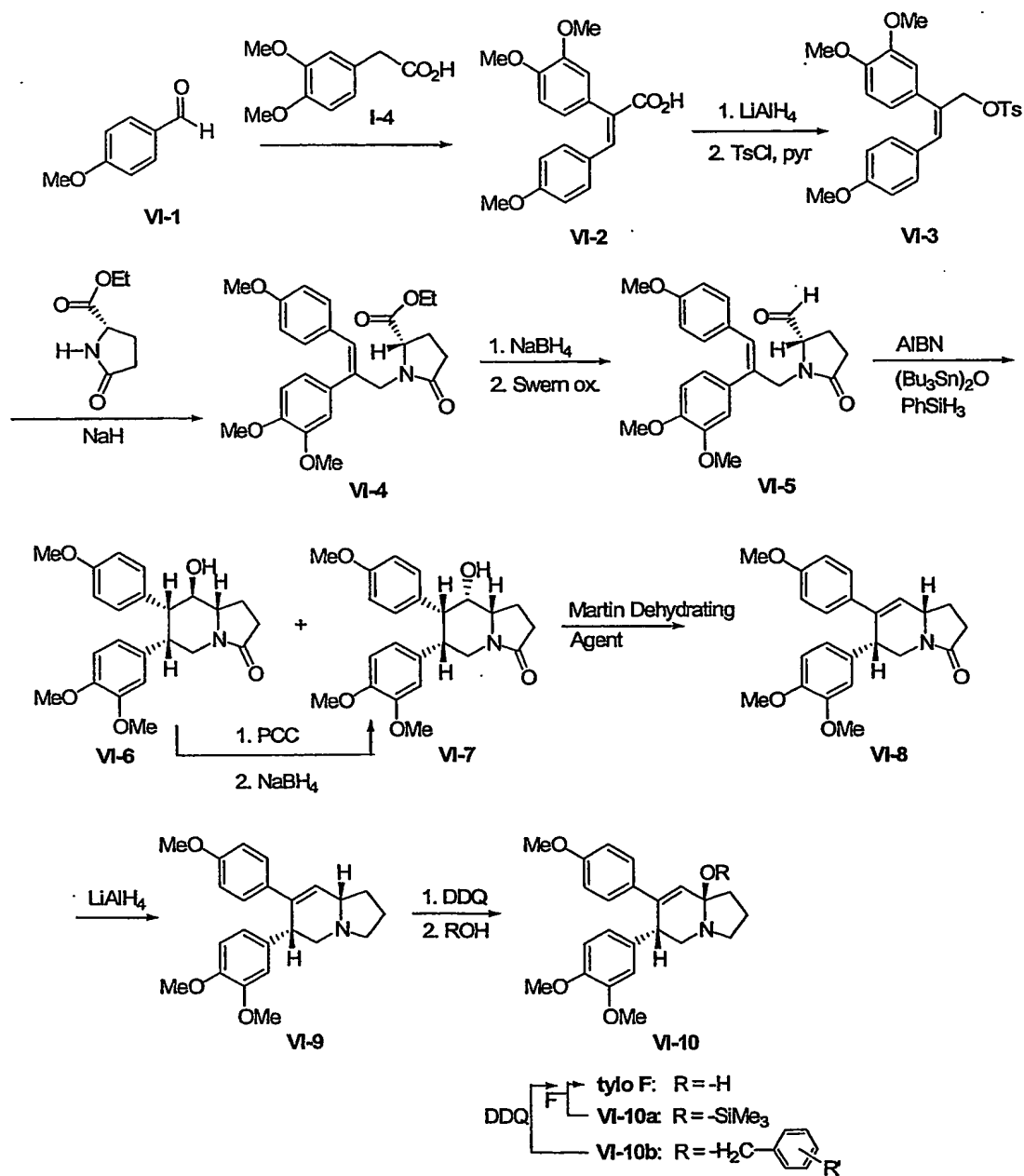
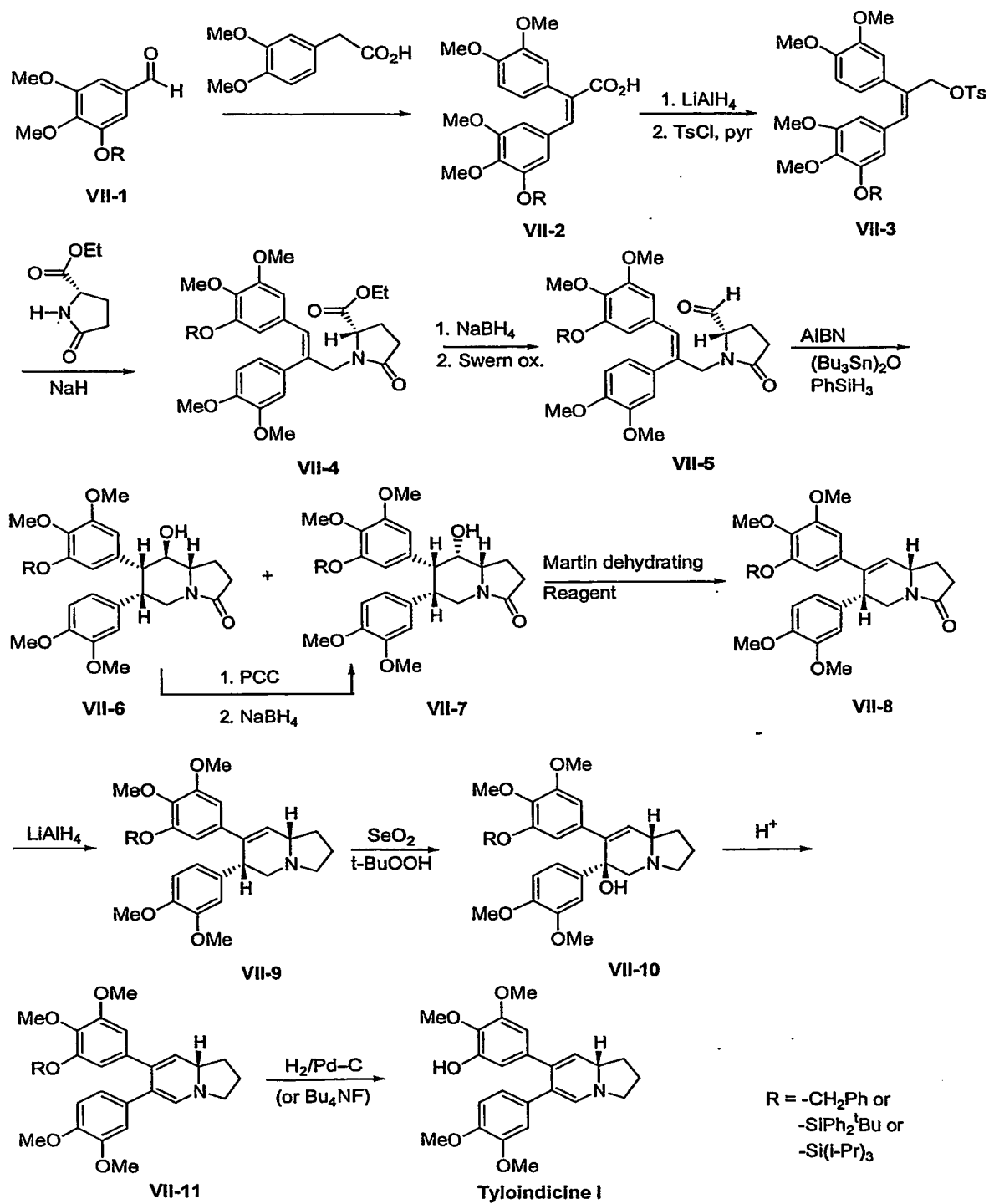




FIGURE 12

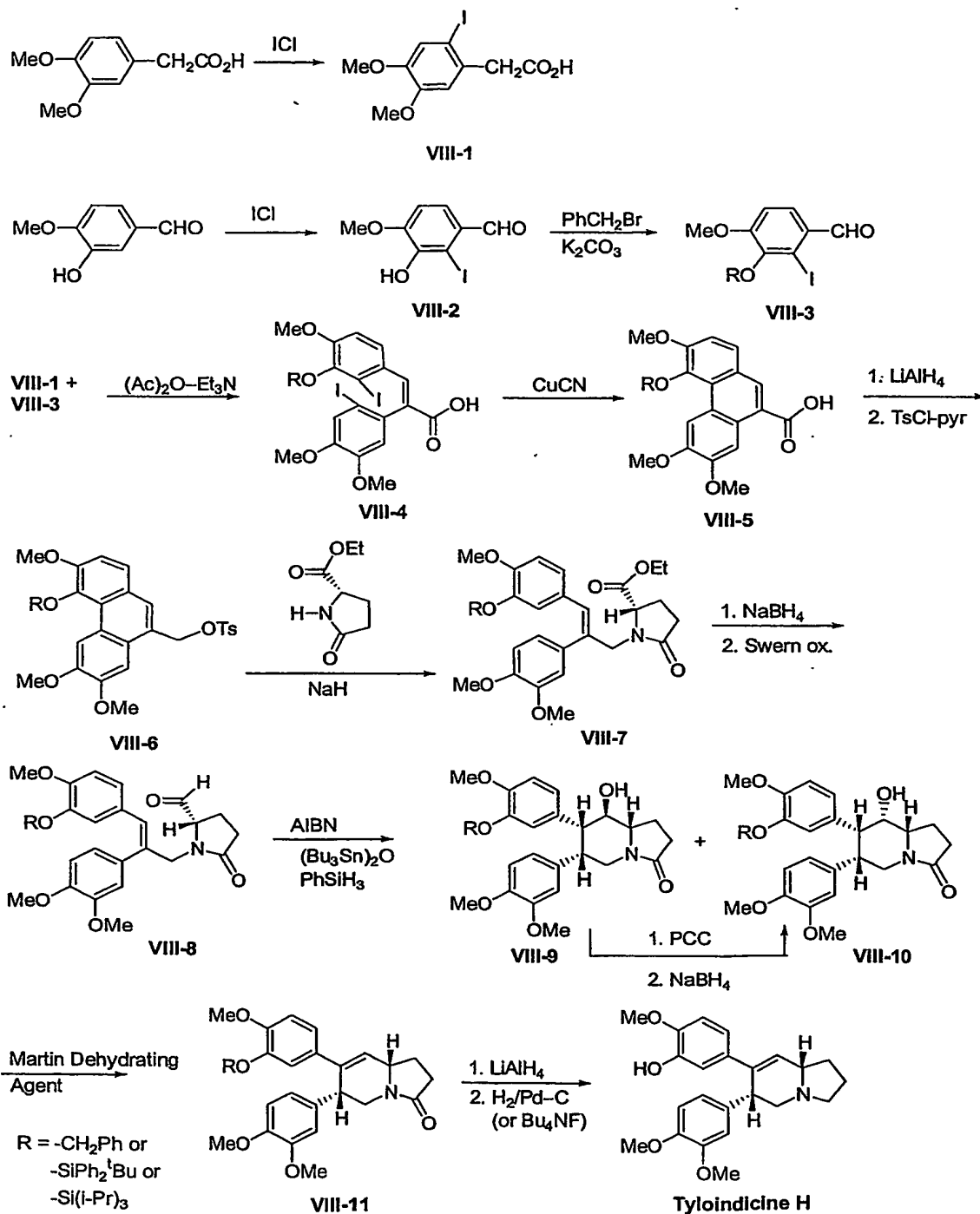
## Scheme VII



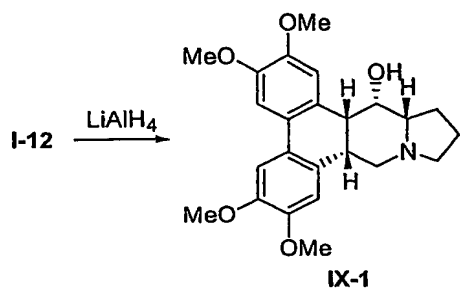
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FIGURE 13

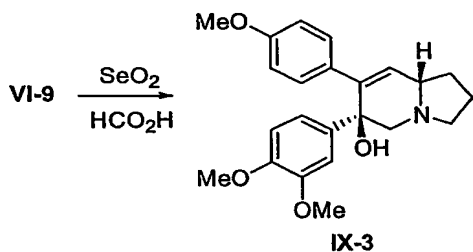
## Scheme VIII



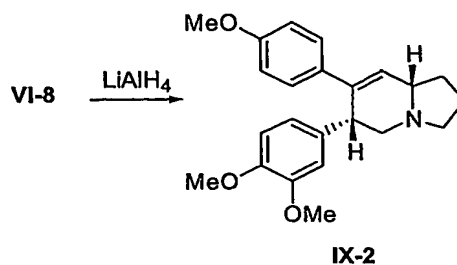
## Scheme IX



Gives analogue (epimer) to NSC-717334. Similar conversions possible for VI-6, VI-7, VII-6, VII-7, VIII-9, VIII-10. VII-6, VII-7, VIII-9, VIII-10 can be deprotected, then reduced for additional analogues. A few will be made to search for activity.

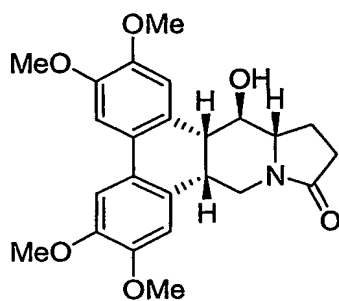


Gives the tylo F analogue of II-3 (NSC-716802, active). VII-10, deprotect. Also LiAlH<sub>4</sub>, SeO<sub>2</sub> on VIII-11, deprotect.



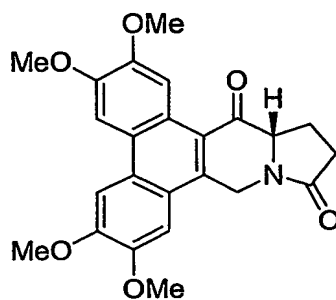
Screen VII-9 and deprotect to give analogue.

FIGURE 15



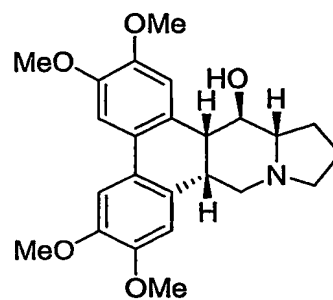
NSC-717334, I-11

(III)



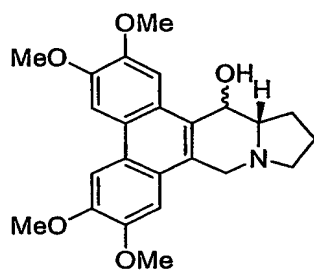
NSC-712822

(IV)



NSC-717336

(V)



II-3a: OH "up" DCB-3501

II-3b: OH "down" DCB-3503, NSC-716802

(VI)

FIGURE 16

## Scheme X

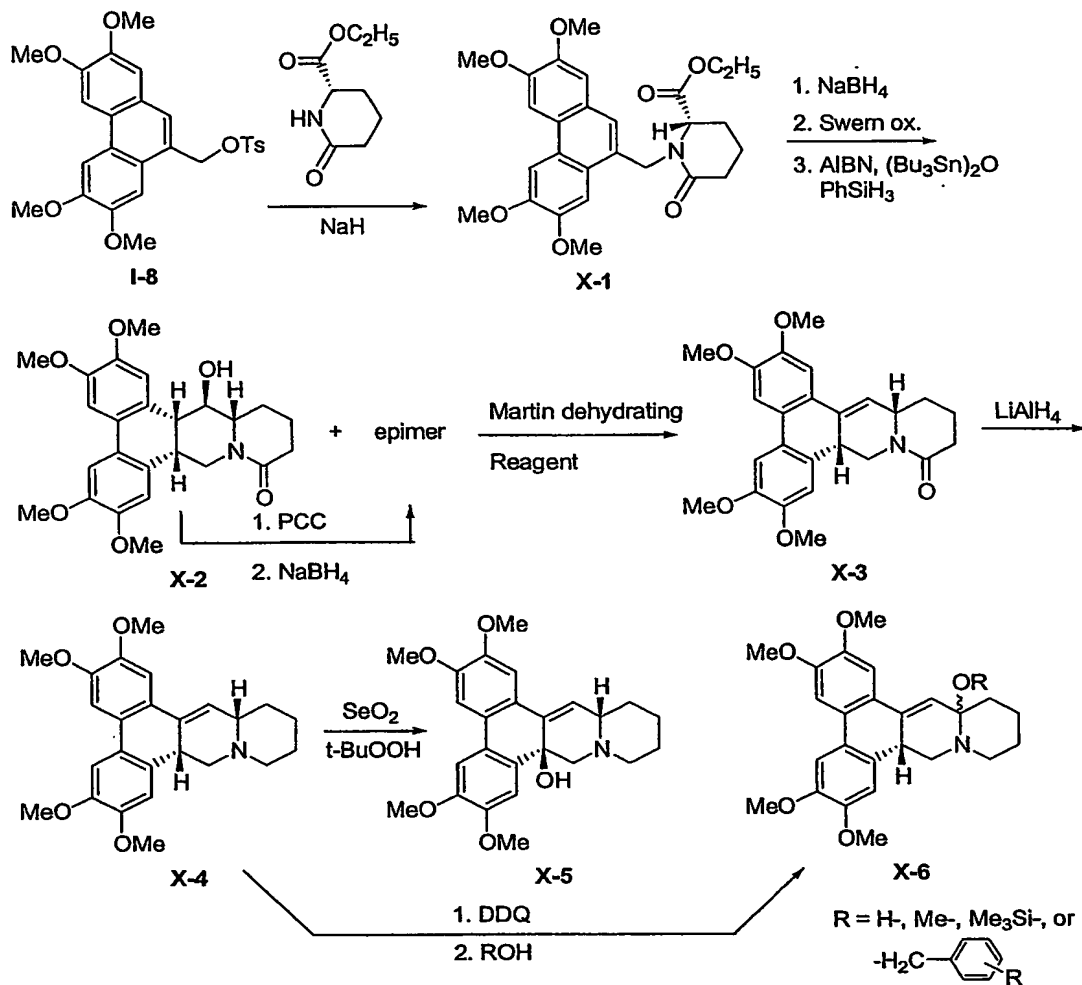


FIGURE 17

## Scheme XI

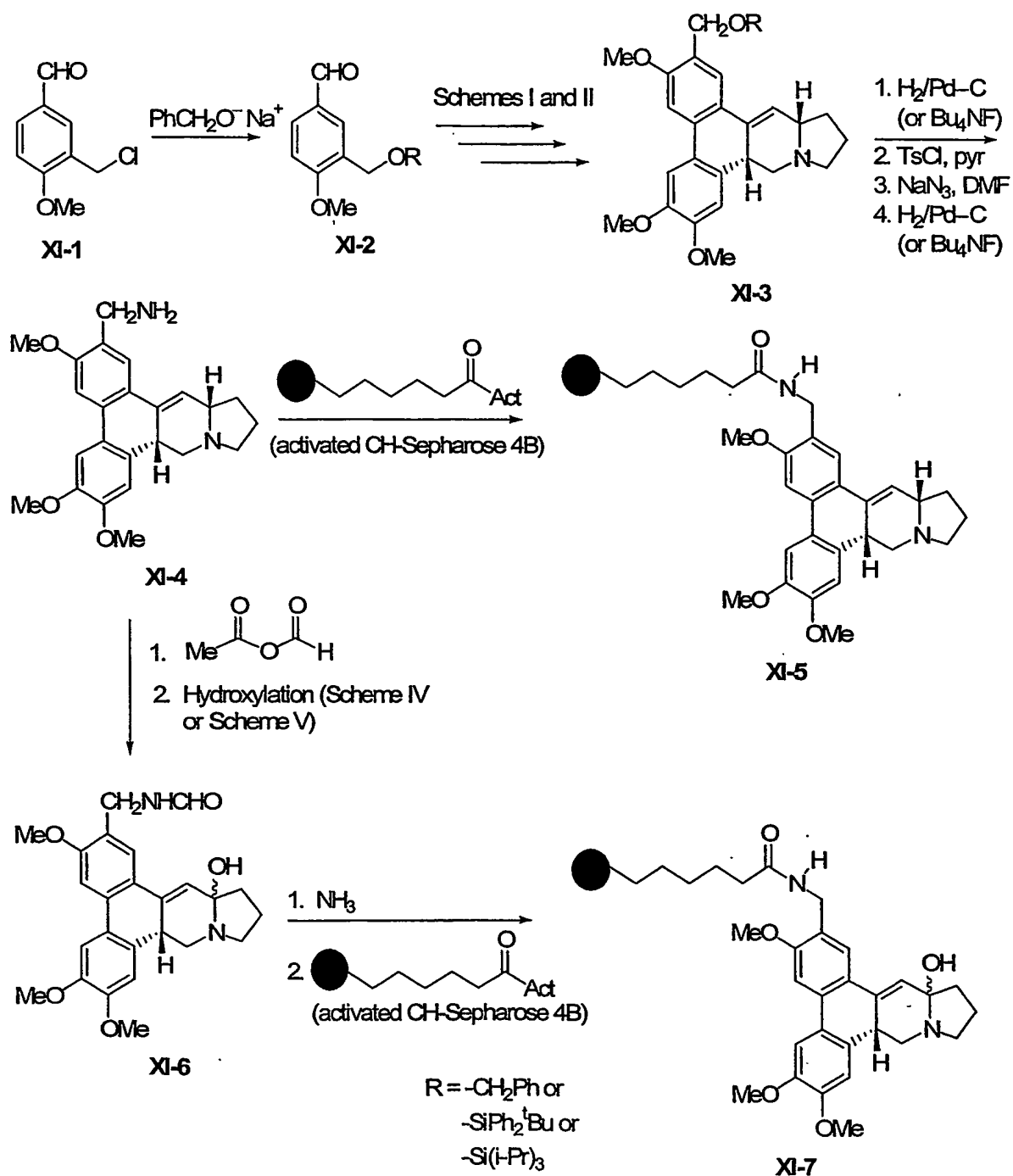


FIGURE 18

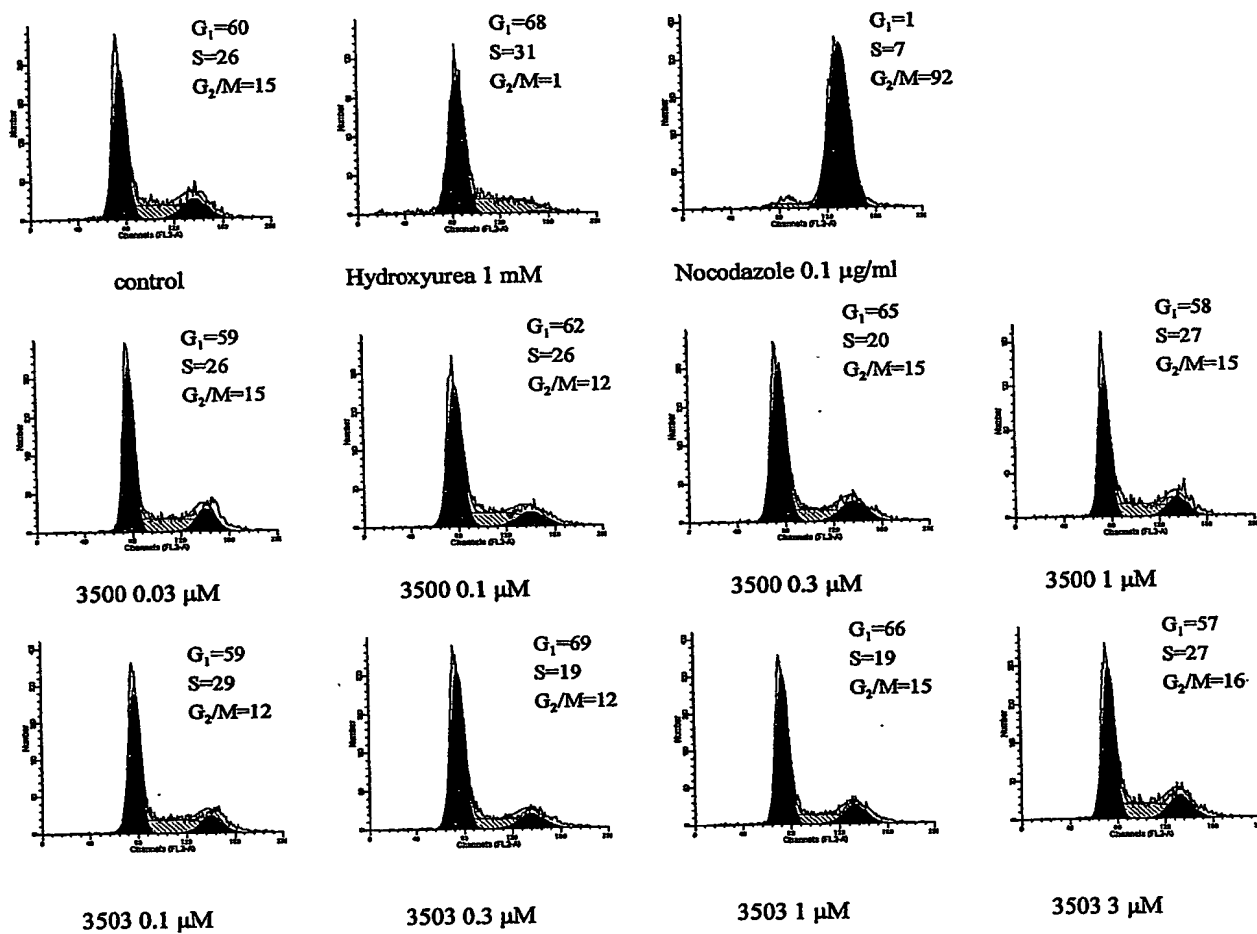
**B. HepG2**

FIGURE 19

### Clonogenic Assays Effect of ZH-152

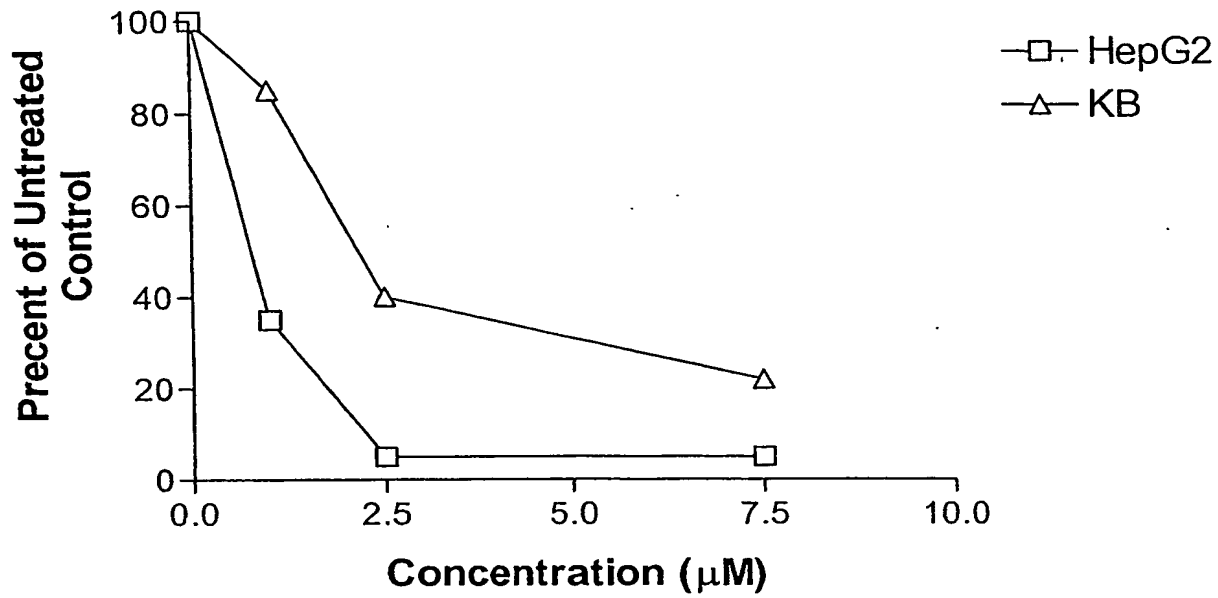
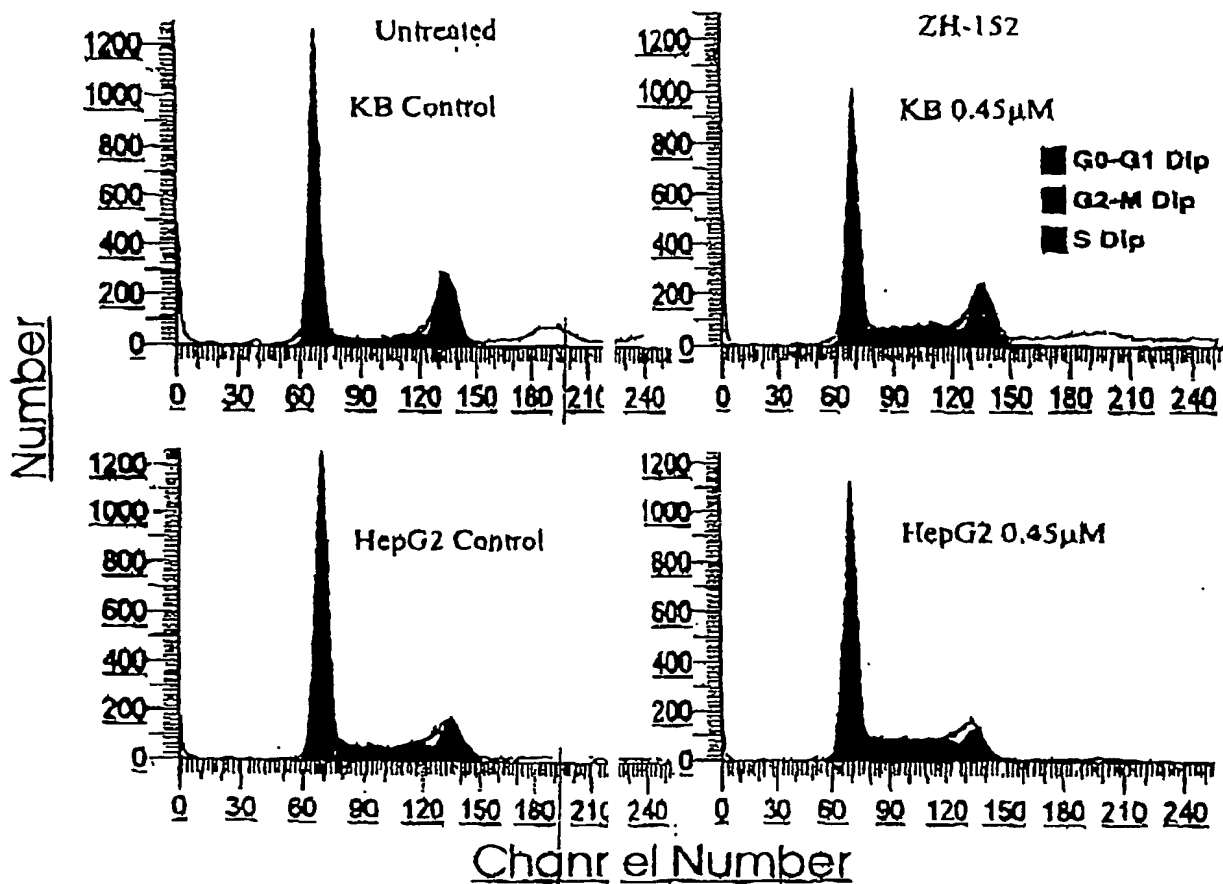




FIGURE 20

Effect of 24h Treatment with ZH-152 on Cell Cycle Progression



ZH-152 slows down the cell progress in S-phase of both cell lines. Thus, the growth inhibition of these two cell lines by ZH-152 is due to the inhibition at targets responsible for S-phase progression. Additional biochemical determinants may play a role in the preferential killing (loss of clonogenicity) of HepG2 to that of KB.

FIGURE 21

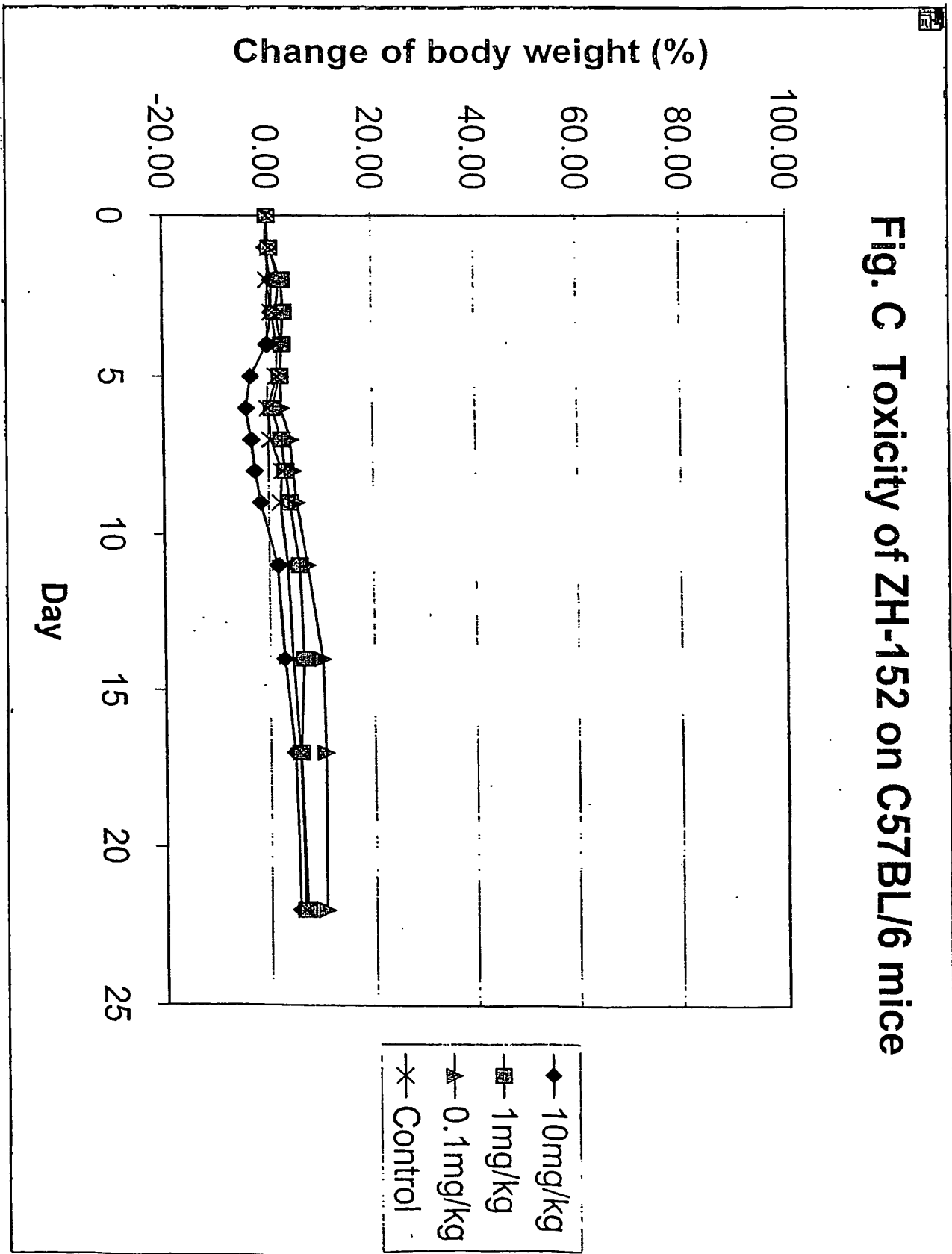


FIGURE 22

